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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/687,993 | 10/13/2000 | Shaw-Fen Sylvia Hu | A-357C | 2749 |

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US Patent Operations DRC
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| EXAMINER |
|---|
| HAYES, ROBERT CLINTON |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/687,993 | Applicant(s) Hu |
|---|---|---|
| | Examiner Robert C. Hayes, Ph.D. | Art Unit 1647 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Oct 18, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *31, 32, and 45-49* is/are pending in the application.

4a) Of the above, claim(s) *32 and 46-49* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31 and 45* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *31, 32, and 45-49* are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restriction*

1. Applicant's election with traverse of Group Ip (claims 31 & 45-49 as it relates to gene therapy using SEQ ID NO:18) in Paper No. 5 is acknowledged. The traversal is on the ground(s) that "the Director **may** require the application to be restricted to one of the inventions [emphasis added]", and that "[i]f the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to independent or distinct inventions [emphasis added]". This is not found persuasive because cell therapy is distinct from gene therapy which requires different starting materials, administration protocols, immuno-rejection considerations, etc., as illustrated by their art recognized differences in classification. Moreover, each different polynucleotide sequence is unique, as illustrated by the unique SEQ ID Nos disclosed, which also would require separate search and examination for each unique sequence. Therefore, a serious burden for searching and examining these distinct inventions would be created for the examiner, for the reasons made of record in Paper No: 4. The requirement is still deemed proper and is therefore made FINAL.

Claims 32 & 46-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

This application contains claims 32 & 46-49 drawn to an invention nonelected with traverse in Paper No. 5. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Claim Rejections - 35 U.S.C. § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31 & 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes various truncated variants of the "human" GDNF polypeptides of SEQ ID No: 2, and the DNA that encodes such. In contrast, the specification fails to describe any polynucleotide molecules that encode polypeptides from any other "non-human" species, or generic allelic variants of the human GDNF polynucleotide species of SEQ ID NO:1. In other words, no adequate written description of what constitutes any different species, allelic variant, or different open reading frame that merely "comprise" fragments of SEQ ID NO:1, or that comprise sequences that code generic heterologous polypeptides (i.e., as currently interpreted by the recitation of "encoding", etc.) fused to random fragments of SEQ ID

NO:2, are provided within the instant specification; especially when the specification fails to describe what critical encoded amino acids define any distinguishable and assayable GDNF function/activity. Nor could one skilled in the art reasonably visualize what constitutes such generic heterologous DNA molecules encompassed by these claims, as currently and broadly claimed; thereby, not meeting the written description requirements under 35 U.S.C. 112, first paragraph.

It is suggested that amending the claims to "administering a polynucleotide consisting of a polynucleotide sequence encoding a truncated... GDNF... selected from [the group] SEQ ID NO:18" may obviate this rejection.

Applicant is directed toward the Revised Interim Utility and Written Description Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

3. Claims 31 & 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing survival of dopaminergic neurons with structurally defined GDNF polypeptides, does not reasonably provide enablement for any *in vivo* method for increasing survival of unknown populations of neurons with structurally uncharacterized GDNF polypeptides using gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification proposes a method of increasing survival of dopaminergic neurons or increasing dopamine uptake in Parkinson's patients (e.g., pages 1-2 of the specification) using human GDNF. However, no description of successfully using gene therapy to accomplish such is disclosed, nor known in the art. Nor would all neuronal populations be expected to contain receptors for human GDNF, and therefore, be targets for gene therapy. Accordingly, page 2 of the specification states that "[a] given neurotrophic factor, in addition *to having the correct neuronal specificity*, must be available in sufficient quantity to be used as a pharmaceutical treatment [emphasis added]". Therefore, because the art recognizes that only dopaminergic neurons are responsive to GDNF, and because only dopaminergic neurons are shown within the specification to be responsive to GDNF, it would require undue experimentation for the skilled artisan to discover what other putative neuronal populations, if any, may also be responsive to GDNF, as currently claimed.

Second, the state of the art is such that numerous problems exist concerning effective *in vivo* "affecting the survival or function of neurons", because neuronal cell damage often results in cell death, and because even "administration" of neurotrophic factors to treat neurons requires solutions to not only bypassing the blood-brain barrier when treating CNS disorders but to selectively target responsive cells, if known, with enough neurotrophic factor to elicit any response (i.e., through specific receptor binding; see page 2 of the specification). In other words, "effective" *in vivo* administration, as it relates to treating any neuronal cell type with any protein, or DNA encoding a protein, requires that one skilled in the art must know how, when or where

the proposed invention is to be administered. In contrast, the instant specification has failed to disclose how these parameters are to be determined, what other specific neuronal populations are responsive to the GDNF polypeptides/polynucleotides of the instant invention, how a similar disclosed method was practiced in the art with a different agent, or to provide even a single *in vivo* working example of the claimed method. In other words, it cannot be successfully extrapolated from the limited *in vitro* tissue cultures disclosed using 15 day old embryonic rat substantia nigra neurons (which merely involve administering GDNF proteins, versus gene therapy as claimed), whether the skilled artisan has successfully practiced Applicant's invention without requiring undue experimentation to first discover how to make and use Applicants' invention, as currently claimed; especially as it relates to determining the metes and bounds for "affecting... [unknown] function[s] of [unknown] neurons" that alternatively encompass regeneration and resurrection of dead neurons (i.e., "functions") that do not reasonably occur (e.g., see Jackowski, pg. 305, last *pp*).

Third, the unpredictability of the art related to gene/cell therapy, is as illustrated by the 1995 "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" which states that:

"While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in *any gene therapy protocol*, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

Significant problems remain in all basis aspects of gene therapy. Major difficulties at the basic level include *shortcomings in all current gene transfer vectors* and an *inadequate understanding of the biological interaction of these vectors with the host"* [emphasis added; page 1].

In other words, the unpredictability within the art in treating any generic neuron *in vivo* is compounded by the unpredictability within the art regarding successfully practicing any gene therapy protocol, as required to practice the instant invention, especially when attempting to affect unknown and undescribed neuronal populations and attempting to "affect" unknown neuronal "functions" using the currently inadequately defined polynucleotides encoding fragments of a functional GDNF polypeptide; thereby, reasonably requiring undue experimentation for the skilled artisan to known how to make and use the invention as currently claimed.

4. Claims 31 & 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds envisioned by the recitation "function of neurons" to be "affected" is unknown since it is unknown if increasing or decreasing a particular assayable function is envisioned, or even what exact "function" to be "affected" is intended; thereby, being indefinite.

***Conclusion***

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
January 13, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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